REMARKS

Pending Claims and Amendments Herein

Claims 95-106 are pending, and Claims 1-94 have been withdrawn from consideration. Claims 1-94 are canceled herein as directed to the nonelected invention, without prejudice as to their pursuit in another co-filed application. Claim 95, 96, 101, 102, 104, and 105 were amended to correct minor matters of form, e.g., to provide antecedent basis, or to amend to proper Markush group format. The specification has been amended pursuant to the Examiner's request. The claim and specification amendments are fully supported by the specification as originally filed.

The Office Action

The Office Action sets forth a single rejection of the subject application. Claims 95-106 are rejected under 35 U.S.C. § 103 over Bergmann et al. (U.S. Patent 5,541,116) in view of each of Chen (U.S. Patent 6,525,102) and Flaa (PCT International Application WO 96/27661). Applicants request that the Examiner reconsider the grounds for rejection as discussed in the following paragraphs.

Nonobviousness of the Application Claims

The Office Action alleges that claims 95-106 are obvious over Bergmann et al. in view of each of Chen and Flaa. The Office Action acknowledges that Bergmann et al. fails to teach the pH limitations of the independent claims of the subject application, as well as the additional stabilizing substances set forth in some of the dependent claims. The Office Action argues, however, that it would have been obvious to stabilize peptides as taught by Bergmann et al. at the pH ranges and with the additional substances taught by each of Chen and Flaa because both Chen and Flaa teach stabilizing various polypeptides for the same function as claimed at the pH range and with the substances as presently claimed. This rejection is respectfully traversed.

Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, both a suggestion to make the composition or carry out the claimed process, and a reasonable expectation of success must be found in the prior art to support a conclusion that a patent application claim is obvious. *In re Vaeck,*

947 F.2d 488, 493 (Fed. Cir. 1991). An invention is not obvious over the prior if the prior art does not suggest each and every limitation of the claim. Under § 103, a prior art reference that fails to teach toward the claimed invention, or teaches away from the claimed invention, will not render the invention as claimed obvious. The application of the law to the facts of this case are discussed below.

a. Failure of the references to suggest all the claim limitations

There is nothing in the disclosure of Bergmann et al. alone or in combination with that of Chen and Flaa to teach or suggest a method of obtaining (a) a "stabilized test sample", and/or (b) that has a pH "of from about 4.0 to about 6.5", and the Office Action does not provide any evidence to the contrary.

Bergmann et al. relies for stabilization of blood peptides in patient samples on the addition of a combination of the proteolysis inhibitors amastin and leupeptin and ethylenediaminetetraacetic acid (EDTA). By contrast, in the method of stabilizing a test sample according to the invention, the use of proteolysis inhibitors in the test sample is optional (e.g., discussed at page 18, lines 9-15). As discussed in the subject application, "the key to the stability of the test samples of the present invention is pH" (page 20, lines 1-2). Bergmann et al. thus in no way teaches or suggests the criticality in test samples of having a pH "of from about 4.0 to about 6.5" for stabilization of the natriuretic peptide.

The secondary references Chen and Flaa provide no teachings which cure the deficit of Bergmann et al. Chen discloses stabilization of aqueous pharmaceutical compositions of polypeptides by avoiding the problem of polypeptide aggregation and/or deamidation (glutamine or asparagine) by inclusion in the pharmaceutical composition of the combination of an amino acid base buffered by an acid substantially free of its salt form. Chen clearly recognizes that the optimum pH for stability of a particular polypeptide of interest needs to be determined empirically (e.g., column 10, lines 1-7). Chen provides no information, however, regarding the optimum pH for stability of natriuretic peptides in a test sample.

Likewise, Flaa provides no more than a broad brush teaching that an artificial matrix can be derived for troponin, myoglobin, CK, CK isoenzymes, LD, LD isoenzymes,

myosin, and fragments thereof, and speculates that such a matrix can be derived for other cardiac markers. A chelating agent in the matrix is required by Flaa (e.g., page 7 lines 18-24, and page 10, lines 23-29), and includes EDTA. Such chelating agents of Flaa thus appear to correspond to the proteolysis inhibitors of Bergmann et al., which means Flaa adds little, if anything, over the teachings of Bergmann et al. Flaa, like Chen, fails to provide information regarding the optimum pH for stability of natriuretic peptides in a test sample.

In sum, the teachings of Bergmann et al., Chen, and Flaa considered in combination would do no more than, at best, invitie one to further experimentation on method for stabilizing test samples containing natriuretic peptides. Such obviousness to ***try*** to obtain the subject invention is not obviousness under 35 U.S.C. § 103. The references alone or in combination fail to teach or suggest a method of obtaining (a) a "stabilized test sample", and/or (b) that has a pH "of from about 4.0 to about 6.5", as is required for a finding of obviousness.

b. Lack of motivation to combine the prior art's teachings

Bergmann et al. provides a means for stabilization in ***blood samples***, Chen discloses stabilization of ***aqueous pharmaceutical compositions***, and Flaa provides at best stabilization in an ***artificial matrix***. Bergmann et al. provides for stabilization by inclusion of proteolysis inhibitors, Flaa by inclusion of a specific type of proteolysis inhibitor (chelating agents such as EDTA), and Chen by the combination of an amino acid base buffered by an acid substantially free of its salt form. The three references thus use distinctly different liquid compositions along with different methods of addressing the issue of stabilization. Based on this, one of ordinary skill clearly would lack motivation to combine the disclosure of Bergmann et al. with the teachings of Chen and Flaa. Of course, absent such motivation to combine, the obviousness rejection is not supported.

c. The prior art's teaching away from the subject invention

Moreover, the prior art disclosures in fact defy combination such that the subject invention can be obtained. This is because Bergmann et al. in its reliance for

stabilization on proteolysis inhibitors, Flaa in its reliance of chelating agents, and Chen in its reliance on the combination of an amino acid base buffered by an acid substantially free of its salt form, ***teach away*** from the subject invention. Even if the teachings are combined, the closest to the invention that is obtained are test samples in which the natriuretic peptide is stabilized by proteolysis inhibitors and which arguably fall within the pH range recited in the claims and may include additional stabilizing substances set forth in some of the dependent claims. This is not the subject invention.

For at least the reasons given above, applicants respectfully submit that the obviousness rejection is unwarranted and request that it be withdrawn.

Other Matters

The Abstract was objected to because it was not directed to the presently claimed invention. Applicants have rewritten the Abstract so that it is directed to the presently claimed invention.

The Examiner requested that Applicants inform the Examiner of related applications, patented, pending or abandoned. The subject application is a continuation-in-part application of U.S. Patent Application 10/620,475 (7098US01), currently pending. U.S. Patent Application 11/248,650 (7098USC1) is a divisional application of U.S. Patent Application 10/620,475, and is also currently pending (allowed). Applicants' undersigned counsel regrets the prior error in not correctly identifying the relationship between these applications (e.g., in the Amendment filed January 18, 2007 in the '650 application, which will be correctly amended prior to payment of the issue fee).

The Examiner also requested that Applicants inform the Examiner as to how the present CIP application differs from the parent application. As described previously by applicants (e.g., Response filed January 19, 2006), the subject patent application contains patent claims directed to stable test samples and methods of making the same for use in determining the quantity of natriuretic peptide contained in the sample, and so differs from the '650 and '475 application, which among other differences, do not contain these claims.

CONCLUSION

For at least the foregoing reasons discussed above, the subject application is believed to be in good and proper form for allowance. The Examiner is therefore requested to pass this application to issue. If, in the opinion of the Examiner, a telephonic interview would expedite the prosecution of the present application, the Examiner is invited to contact applicants' undersigned attorney.

Respectfully submitted,
Parsons, *et al.*

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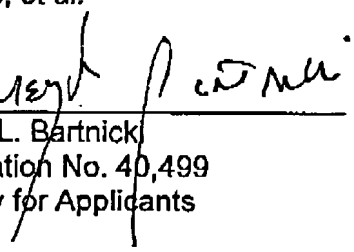

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PATENT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant: Parsons, *et al.*

Serial No.: 10/721,031

Filed: November 24, 2003

For: STABLE COMPOSITIONS FOR MEASURING HUMAN NATRIURETIC PEPTIDES

Case No.: 7098.US.P1

Group Art No.: 1655

Examiner: Gitomer, Ralph J.

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TRANSMITTAL LETTER

Dear Sir or Madam:

Enclosed herewith for the patent application identified above is the following:

- Amendment and Response (9 Pages).

The Commissioner is hereby authorized to charge any additional Filing Fees required under 37 CFR §1.16, as well as any patent application processing fees under 37 CFR §1.17 **(including in particular any fees due for the three-month extension of time)**, or other fees associated with this communication for which full payment had not been tendered, to Deposit Account No. 01-0025. A duplicate copy of this sheet is enclosed.

Respectfully submitted,
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